REMARKS

This Amendment is filed in response to the non-final Office Action dated April 17, 2009, and is respectfully submitted to be fully responsive to the rejections raised therein. Accordingly, favorable reconsideration on the merits and allowance are respectfully requested.

In the present Amendment, claims 1-33 have been canceled. Claims 34 and 35 have been amended to replace "derivative" with the term compound. Claim 34 has also been amended to recite that the anti-inflammatory drug is selected from the group consisting of a non-steroidal anti-inflammatory drug and a disease modifying anti-inflammatory drug.

Claims 36-57 have been newly added. Specifically, claims 36, 38, 41, 42, and 44-57, represent original claims 9, 10, 7, 12, and 14-27, respectively, with the exception that the term "derivative" (recited in the original claims) is excluded from the claim language in the new claims.

Claim 37 depends from claim 36 and further characterizes "non-steroidal anti-inflammatory drug". Support for claim 37 can be found in Examples 1, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 20 on pages 36-55 of the specification, for example.

Claims 39 and 40 depend from claims 38 and 36, respectfully. Support for claims 39 and 40 can be found in original claim 11 and the specification on page 26, lines 1-8 and page 27, lines 2-5, for example.

Claim 43 depends from claim 36 and further characterizes the hyaluronic acid compound. Support for claim 43 can be found in original claim 13 and in the specification on page 4, lines 20-22, for example.

No new matter has been added. Entry of the Amendment is respectfully submitted to be proper. Upon entry of the Amendment, claims 34-57 will be all the claims pending in the application.

I. Information Disclosure Statement

The following six (6) foreign documents cited on the International Search Report (ISR) for PCT/JP05/0000125, were cited on Form SB/08 and submitted with the IDS filed on July 7, 2006: WO 1999/059603, JP 62-64802, JP 63-105003, WO 1992/006714, JP 09-188705, and JP 06-72893. However, these references were not considered by the Examiner because, according to the Examiner, copies of these foreign patent documents and/or translations were not provided to the Office.

Applicants respectfully submit that the SB/08 filed July 7, 2006 listed references cited on the ISR. Since it appears that the International Bureau (IB) did not provide copies of the references to the U.S. Patent and Trademark Office, Applicants provide herewith copies of the above-mentioned documents (see attachment). Consideration of these documents by the Examiner is respectfully requested along with a signed copy of the SB/08 form listing the above-mentioned documents.

II. Election/Restriction

Applicants elected as a provisional species election (i) a non-steroidal anti-inflammatory drug, (ii) diclofenac; and (iii) the compound of Formula (1) wherein Y-CO- is hyaluronic acid, R^1 is a linear hydrocarbon group having two carbon atoms which may have a substituent, R^2 is a

non-steroidal anti-inflammatory drug residue represented by Formula (2), and n is an integer of from 1 to 3. Examiner Goon asserted that in Formula (2), Applicants elected the compound wherein "R^3 is diclofenac [sic], R^4 and R^5 each represent a hydrogen atom, and X represents a chlorine atom."

Applicants respectfully submit that the Examiner's interpretation of the election is not correct. Applicants reiterate that Applicants elected the species of Formula (2) where the compound is diclofenac, and wherein R^3, R^4 and R^5 each represent a hydrogen atom and X represents a chlorine atom. Applicants respectfully request acknowledgement of the elected species in the next Office Communication.

Furthermore, Applicants respectfully request that claims 34 and 35 be rejoined upon the determination that the product claims (36-57) are allowable.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8 and 12-27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 1-8 and 12-27 have been canceled and therefore the rejection of these claims is moot. Furthermore, Applicants submit that new claims 36-57 are definite. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendments to the claims.

IV. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-9 and 12-27 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claims 1-9 and 12-27 have been canceled and therefore the rejection of these claims is moot. Furthermore, Applicants submit that new claims 36-57, which recite a non-steroidal anti-inflammatory drug as an anti-inflammatory drug and an aminoalkyl alcohol as a spacer, comply with written description under 35 U.S.C. § 112, first paragraph. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection in view of the amendments to the claims.

IV. Rejection Under 35 U.S.C. § 102(b)

Claims 1-3, 5-7 and 19-23 are rejected under 35 U.S.C. §102(b) as being anticipated by EP 1 082 963 (EP '963).

Applicants respectfully traverse and request that the rejection be withdrawn in view of the following remarks.

As an initial matter claims 1-3, 5-7 and 19-23 have been canceled and the rejection is therefore moot. Withdrawal of the rejection is respectfully requested.

The spacer moiety in the present claimed invention is represented by an aminoalkyl alcohol (i.e., $H_2N\text{-}R^1\text{-}(OH)_n$), which is structurally distinct from the spacer moiety in EP '963. Further, the manner in which the spacer links the hyaluronic acid with the drug is different. Specifically, in the present claimed invention, the hyaluronic acid is bonded to a non-steroidal anti-inflammatory drug through a covalent bond, wherein a carboxyl group in hyaluronic acid is bonded with the amino group in the spacer compound to form an amido bond, and the hydroxyl

group in the spacer compound is bonded to the carbonyl group (-CO-) in the drug residue through an ester bond.

In contrast, the spacers described in EP '963 are represented by the formulae C_4H_8NH- and $C_8H_{16}NH$-, which are synthesized from 4,4-diaminobutane and 1,8-diaminooctane, respectively. EP '963 describes a compound wherein both of the covalent bond between the hyaluronic acid and the spacer and the covalent bond between the spacer and the matrix metalloprotease (MMP) inhibitor are amide bonds. Thus, the present claims do not read on the subject matter described in EP '963. Accordingly, newly added claims 36-57 are not anticipated by EP '963.

V. Rejection Under 35 U.S.C. § 103(a)

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP '963, in view of JP 9-188705 to Miyamoto (JP '705, machine translation).

Particularly, the Examiner's position is that EP '963 discloses diclofenac sodium salt, tolmetin sodium salt, sulindac, fenbufen, indomethacin, acemetacin, among others, as examples of arylacetic acid based non-steroidal anti-inflammatory agents that can be used for conjugation to hyaluronic acid in paragraph [0034]. The Examiner concedes that EP '963 does not teach the use of a spacer shorter than 1,4-diaminobutane. Per the Examiner JP '705 cures the deficiency of EP '963. Per the Examiner, since EP '963 teaches the conjugation of hyaluronic acid to non-steroidal anti-inflammatory drugs, such as diclofenac, via a 1,2-diaminobutane spacer, and JP '705 teach that H_2N-(CH_2)n-NH_2 wherein n is preferably 2-18, can be used as a spacer for conjugation of a glycosaminoglycan, such as hyaluronic acid, to a protein, peptide or drug, it

would have been *prima facie* obvious for one of ordinary skill in the art to substitute the spacers disclosed by JP '705 with the spacers disclosed by EP '963. One would have been motivated to make the substitution as it is expected that such a substitution would yield a predictable result. Furthermore, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by JP '705, that conjugation of a peptide, protein or drug to a glycosaminoglycan, such as hyaluronic acid, improves the stability of the peptide, protein or drug when it is in the living body (paragraph 0002).

Applicants respectfully traverse.

Claims 1-27 have been canceled and therefore the rejection of these claims are moot.

Claims 36-57, newly added, are patentable over EP '963 alone and/or in consideration of the teachings of JP '705. As admitted by the Examiner, both EP '963 and JP '705 teach alkyl amino spacers made from a diaminoalkyl, which bind to the hyaluronic acid and drug via amide bonds. The presently claimed invention recites an aminoalkyl alcohol as a spacer. This spacer bonds to the drug via an ester bond. Therefore, the present claimed invention is patentably distinct over the art.

Applicants further submit that hyaluronic acid when bonded to an NSAID via a spacer according to the present invention is effective, wherein when hyaluronic acid is bonded to an NSAID via a spacer according to EP '963, the hyaluronic acid derivative is inactive, as shown in Example 47; *see also*, Fig. 8. In Example 47, the results show that the aminoethanol-diclofenac-introduced sodium hyaluronate solution, which used aminoethanol as a spacer (according to the present invention) showed a remarkable analgesic effect. However, the diaminopropane-

diclofenac-introduced sodium hyaluronate solution, in which diclofenac was introduced through an amide bond (such as the spacers in EP '963), had no effect on the test system of this example.

Thus, the present invention has unexpectedly superior properties as compared to the hyaluronic acid derivative in EP '963. For the above-mentioned reasons, newly added claims 36-57 are patentable over EP '963 alone or combined with JP '705.

VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: October 16, 2009